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(71) Applicants *(for all designated States except US)*: LONZA AG [CH/CH]; Münchensteinerstrasse 38, CH-4052 Basel (CH). MERCK & CO., INC. [US/US]; 126 Lincoln Avenue, Rahway, NJ 07065-0907 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*:–BESSARD, Yves [CH/CH]; Av. Rothorn 14, CH-3960 Sierre (CH). LERESCHE, James, Edward [CH/CH]; Kleegärtenstrasse 25, CH-3930 Visp (CH).

(74) Agents: RITTHALER, Wolfgang et al.; Winter Brandl Fürniss Hübner Röss Kaiser Polte, Alois-Steinecker-Str. 22, D-85354 Freising (DE).

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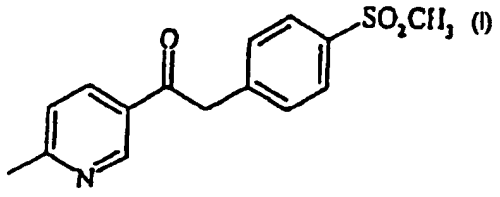
(54) Title: PROCESS FOR PREPARING 1-(6-METHYLPYRIDIN-3-YL)-2-[(4-(METHYLSULPHONYL) PHENYL] ETHANONE



(I)

(57) Abstract: A five-step process for preparing 1-(6-methylpyridin-3-yl) -2-[(4-methylsulphonyl)phenyl] -ethanone of formula (I) described; characterized in that a) 4-(methylthio) benzyl alcohol is converted with hydrochloric acid into 4-(methylthio) benzyl chloride, b) 4-(methylthio) benzyl chloride is converted with an alkali metal cyanide into 4-(methylthio) phenylacetonitrile, c) 4-(methylthio) -phenylacetonitrile is condensed with a 6-methylnicotinic ester to give 3-[2- (4-methylthio) phenyl) -2-cyanoacetyl] (6-methyl) -pyridine, d) 3-[2-(4-methylthio) phenyl)-2-cyanoacetyl] (6-methyl) -pyridine is hydrolysed and decarboxylated under acidic conditions to give 3-[2-(4-methylthio) phenyl) acetyl] (6-methyl) pyridine and, e) 3-[2(4-(methylthio) phenyl) acetyl] (6-methyl) pyridine is oxidized to give the end product. The compound of formula (I) is an intermediate for preparing COX-2 inhibitors, pharmaceutically active compounds having analgesic and antiinflammatory action.

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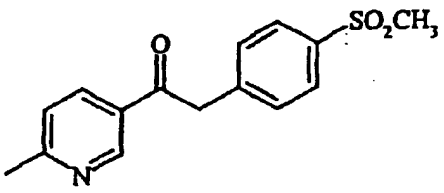
Process for preparing 1-(6-methylpyridin-3-yl)-2-[(4-(methylsulphonyl)phenyl]ethanone

Description

The invention encompasses a novel process for preparing 1-(6-methylpyridin-3-yl)-2-[(4-(methylsulphonyl)phenyl]ethanone of the formula



I

1-(6-methylpyridin-3-yl)-2-[(4-(methylsulphonyl)-phenyl]ethanone is an important intermediate for preparing so-called COX-2 inhibitors, pharmaceutically active compounds having analgesic and antiinflammatory action (R.S. Friesen et al., Bioorganic & Medicinal Chemistry Letters 8 (1998) 2777-2782; WO 98/03484).

The object of the invention was to provide a technically feasible process for preparing the intermediate of the formula I.

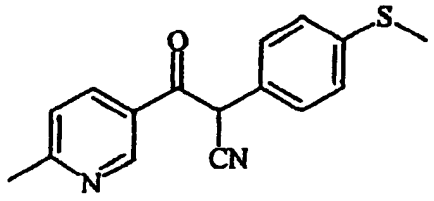
This object was achieved by the novel process according to Claim 1.

The process according to the invention is characterized by five steps, where,

in the first step a), 4-(methylthio)benzyl alcohol is converted with hydrochloric acid into 4-(methylthio)benzyl chloride,

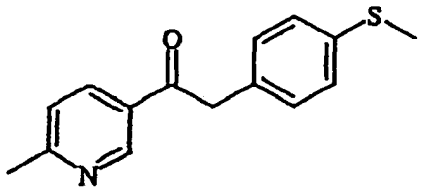
in the second step b), 4-(methylthio)benzyl chloride is converted with an alkali metal cyanide into 4-(methylthio)phenylacetonitrile,

in the third step c), 4-(methylthio)phenylacetonitrile is condensed with a 6-methylnicotinic ester to give 3-[2-(4-(methylthio)phenyl)-2-cyanoacetyl](6-methyl)-pyridine of the formula



II

in the fourth step d), 3-[2-(4-(methylthio)phenyl)-2-cyanoacetyl](6-methyl)pyridine is hydrolysed and decarboxylated under acidic conditions to give 3-[2-(4-(methylthio)phenyl)acetyl](6-methyl)pyridine of the formula



III

and, in the last step e), 3-[2-(4-(methylthio)phenyl)acetyl](6-methyl)pyridine is oxidized to give the end product.

Step a:

The chlorination of 4-(methylthio)benzyl alcohol to 4-(methylthio)benzyl chloride is carried out using hydrochloric acid, advantageously using concentrated hydrochloric acid, at a temperature of from 10°C to 40°C.

The reaction is usually carried out in an organic solvent, advantageously in a water-immiscible solvent, such as, for example, in toluene.

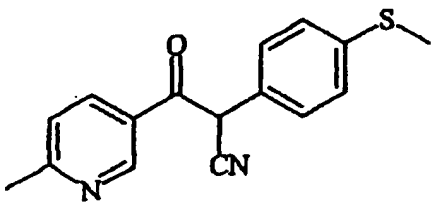
Typically, the chlorination takes about 1 h to 4 h. The 4-(methylthio)benzyl chloride can be obtained in a simple manner by neutralizing the organic phase and removing the solvent. Further purification can be achieved by distillation.

Step b:

The cyanidation of 4-(methylthio)benzyl chloride is carried out using an alkali metal cyanide, advantageously in the presence of a phase transfer catalyst.
Suitable alkali metal cyanides are sodium cyanide or potassium cyanide.
The phase transfer catalysts which can be chosen are known in the art. Suitable are tetraalkylammonium halides, such as, for example, tetra-n-butylammonium chloride or tetra-n-butylammonium bromide.
In general, the reaction is carried out in the presence of a water-immiscible solvent, such as, for example, toluene; if appropriate, water can be added.
The reaction temperature is advantageously from 60°C to 100°C.
After a reaction time of 1 h to 6 h, the product can be isolated in a simple manner from the organic phase by removing the solvent.
Further purification of the product can be achieved by recrystallization from, for example, diisopropyl ether.

Step c:

In the third step, ((methylthio)phenyl)acetonitrile is condensed with a 6-methylnicotinic ester to give 3-[2-(4-(methylthio)phenyl)-2-cyanoacetyl]-(6-methyl)pyridine of the formula

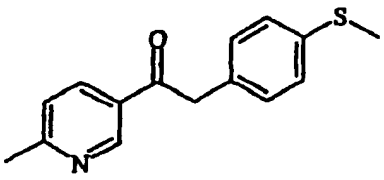


II

The condensation is advantageously carried out in the presence of an alkali metal alkoxide, at a temperature between 60°C and 110°C.
Suitable alkali metal alkoxides are, for example, sodium methoxide or potassium tert-butoxide. The reaction is advantageously carried out in the presence of a lower alcohol or an aromatic hydrocarbon as solvent.
After the condensation, the 3-[2-(4-(methylthio)phenyl)-2-cyanoacetyl](6-methyl)pyridine can be obtained, for example, by adding the reaction mixture to cold water and precipitating the product from the aqueous phase by acidifying it slightly.

Step d:

Hydrolysis and decarboxylation to give 3-[2-(4-(methylthio)phenyl)acetyl](6-methyl)pyridine of the formula



III

are carried out under acidic conditions.
Suitable acids are hydrochloric acid, phosphoric acid or mixtures of acetic acid with a mineral acid.
Advantageously, a mixture of acetic acid and a mineral acid is employed, at a temperature of from 50°C to 115°C.

Particular preference is given to mixtures of acetic acid with concentrated hydrochloric acid or mixtures of acetic acid with concentrated sulphuric acid. If appropriate, a certain amount of water can be added to the mixtures.

Good results were obtained using mixtures of acetic acid/concentrated hydrochloric acid 1:3 or acetic acid/concentrated sulphuric acid/water 1:1:1.

After a reaction time of about 1 h to 20 h, the mixture can be neutralized using, for example, an aqueous ammonia solution, as a result of which the product precipitates out and can be isolated in a simple manner.

Step e:

Oxidation of 3-[2-(4-(methylthio)phenyl)-acetyl](6-methyl)pyridine to the end product is advantageously carried out using hydrogen peroxide in the presence of an alkali metal tungstate, at a temperature of from 10°C to 40°C, preferably at about 20°C.

A particularly suitable alkali metal tungstate is sodium tungstate of the formula $Na_2WO_4.2H_2O$. The alkali metal tungstate is generally employed in catalytic amounts of from 0.5 mol% to 20 mol%, based on the 3-[2-(4-(methylthio)phenyl)acetyl](6-methyl)pyridine used. The reaction is advantageously carried out in the presence of a lower alcohol as solvent. After a reaction time of about 1 h to 6 h, the end product can be precipitated out by addition of water and then be isolated without any problems.

Examples

Preparation of 4-(methylthio)benzyl chloride

Under an atmosphere of nitrogen, 78.7 g (500 mmo)l [sic] of 4-(methylthio)benzyl alcohol were dissolved in 154.5 g of toluene. 131.6 g, (1.3 mol) of conc. HCl were added, and the mixture was stirred at 20-25°C for 30 min. After 2 h (no starting material left according to TLC), the reaction mixture was diluted with 349 g of toluene and the aqueous phase was separated off. The organic phase was neutralized using 14.0 g of $NaHCO_3$ and, after 15 min, filtered, and the solvent was evaporated. The residue that remained consisted of 107.4 g of a yellow oil with toluene, corresponding to a yield of >95% (according to NMR).

^{1}H-NMR ($CDCl_3$):	7.30 (2H,d);
	7.22 (2H,d);
	4.55 (2H, s);
	2.47 (3H, s).
^{1}H-NMR (DMSO):	7.37 (2H,d);
	7.25 (2H, d);
	4.73 (2H,d);
	2.47 (3H,s).

Preparation of 4-(methylthio)phenylacetonitrile

Under an atmosphere of nitrogen, 25.9 g (150 mmol) of 4-(methylthio)benzyl chloride were dissolved in 45.5 g of toluene. 9.29 g (180 mmol) of sodium cyanide, 0.92 g (2.9 mmol) of tetrabutylammonium chloride and 14.4 g of water were then added. The mixture was stirred at 80-85°C for 2 h. The reaction mixture was admixed with 30 g of toluene and 45 g of water, the aqueous phase was decanted off and the organic phase was concentrated. This gave a residue of 24.6 g of the title product in a yield of >95% (according to NMR) in the form of a pink solid.

^{1}H-NMR ($CDCl_3$): 7.25 (4H,m);
3.70 (2H,s);
2.47 (3H,s).

Preparation of 3-[2-(4-(methylthio)phenyl)-2-cyanoacetyl](6-methyl)pyridine

Under an atmosphere of nitrogen, a mixture of 38.5 g (250 mmol) of ethyl 6-methylnicotinate, 29.9 g (500 mmol) of sodium methoxide (90.5%) and 300 ml of toluene was added, at 85-90°C and over the course of 30 min, to a solution of 47.3 g (250 mmol) of 4-(methylthio)phenylacetonitrile in 75 ml of toluene. This mixture was stirred under reflux for 14 h, then distilled until the overhead temperature exceeded 110°C and kept at reflux for another 6 h. The reaction mixture was poured into 500 g of ice water, the organic phase was decanted off and the aqueous phase was extracted with 3 x 100 ml of toluene. The aqueous phase was acidified to pH 6.0 using conc. HCl. The resulting yellow-beige suspension was filtered and the residue was washed with water and dried. This gave 53.9 g (76%) of the title product in the form of a yellow solid.

^{1}H-NMR ($CDCl_3$): 9.00 (1H,s);
8.10 (1H,d);
7.3 (5H,m);
5.45 (1H,s);
2.60 (3H,s);
2.45 (3H,s).

Preparation of 3-[2-(4-(methylthio)phenyl)acetyl]-(6-methyl)pyridine

A mixture of 8.0 g (28 mmol) of 3-[2-(4-(methylthio)phenyl)-2-cyanoacetyl](6-methyl)pyridine, 20 ml of acetic acid and 60 ml of concentrated hydrochloric acid was heated at 95°C to 100°C for 1.5 h.

The orange solution was cooled and adjusted to pH 10 using concentrated ammonia solution. The resulting yellow-beige suspension was filtered and the residue was washed with water and dried. This gave 5.35 g (74%) of the title product in the form of a yellow solid.

^{1}H-NMR ($CDCl_3$): 9.10 (1H,s);
8.15 (1H,d);
7.2 (5H,m);
4.21 (2H,s);
2.61 (3H,s);
2.45 (3H,s).

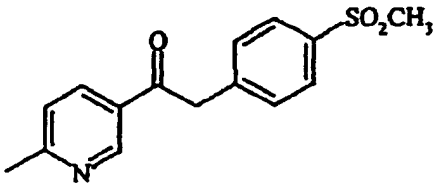
Preparation of 1-(6-methylpyridin-3-yl)-2-[(4-(methylsulphonyl)phenyl]ethanone

Under an atmosphere of nitrogen, a suspension of 8.9 g (34.5 mmol) of 3-[2-(4-(methylthio)phenyl)-acetyl](6-methyl)pyridine in 90 ml of methanol was heated to 55°C and adjusted to pH 4.5 using 2 N sulphuric acid. An aqueous solution of 0.22 g (0.7 mmol) of sodium tungstate in 7 ml of water was then added. At 55°C, 10 mol of hydrogen peroxide were then added over the course of 1 h, and the mixture was then cooled to room temperature and filtered. The slightly beige filtration residue was washed using 2 x 30 ml of a mixture of water/isopropanol 2:1 and 2 x 30 ml of water and then dried under reduced pressure at room temperature. This gave 7.43 g of the title product in a yield of 75%.

^{1}H-NMR ($CDCl_3$): 9.15 (1H,s);
8.18 (1H,d);
7.92 (2H,d);
7.47 (2H,d);
7.30 (1H,d);
4.39 (2H,s);
3.04 (3H,s);
2.63 (3H,s).

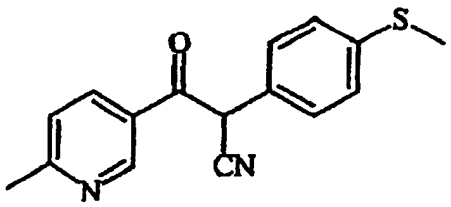
Patent claims

1. Process for preparing 1-(6-methylpyridin-3-yl)-2-[(4-(methylsulphonyl)phenyl]ethanone of the formula



I

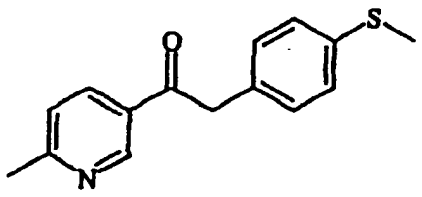
characterized in that
in the first step a), 4-(methylthio)benzyl alcohol is converted with hydrochloric acid into 4-(methylthio)benzyl chloride,
in the second step b), 4-(methylthio)benzyl chloride is converted with an alkali metal cyanide into 4-(methylthio)phenylacetonitrile,
in the third step c), 4-(methylthio)-phenylacetonitrile is condensed with a 6-methylnicotinic ester to give 3-[2-(4-(methylthio)phenyl)-2-cyanoacetyl](6-methyl)-pyridine of the formula



II

in the fourth step d), 3-[2-(4-(methylthio)phenyl)-2-cyanoacetyl](6-methyl)-pyridine is hydrolysed and decarboxylated under acidic conditions to give 3-[2-(4-

(methylthio)phenyl)acetyl](6-methyl)pyridine of the formula



III

and, in the last step e), 3-[2-(4-(methylthio)phenyl)acetyl](6-methyl)pyridine is oxidized to give the end product.

2. Process according to Patent Claim 1, characterized in that the reaction in step a) is carried out at a temperature of from 10°C to 40°C and in an organic solvent.

3. Process according to Patent Claim 1 or 2, characterized in that the reaction in step b) is carried out in the presence of a phase transfer catalyst.

4. Process according to any of Patent Claims 1 to 3, characterized in that the reaction in step b) is carried out at a temperature of from 60°C to 100°C.

5. Process according to any of Patent Claims 1 to 4, characterized in that the condensation in step c) is carried out in the presence of an alkali metal alkoxide at a temperature between 60°C and 110°C.

6. Process according to any of Patent Claims 1 to 5, characterized in that the hydrolysis and decarboxylation in step d) is carried out using a mixture of acetic acid and a mineral acid, at a temperature of from 50°C to 115°C.

7. Process according to any of Patent Claims 1 to 6, characterized in that the oxidation in step e) is carried out using hydrogen peroxide in the presence of an alkali metal tungstate, at a temperature of from 10°C to 40°C.

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/EP 00/06825

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D213/50

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
BEILSTEIN Data, EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	BURGER A. & WALTER JR., C.R.: "Some .alpha.-substituted .beta.-pyridylethylamines" THE JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 72, no. 5, May 1950 (1950-05), pages 1988-1990, XP002128997 * compounds XII and XIII * page 1990, left-hand column	1-7
Y	US 3 717 647 A (VILLANI F.J.) 20 February 1973 (1973-02-20) column 10, line 1 - line 20 column 12, line 1 - line 15	1-7
Y	US 4 115 578 A (MILLER G.A. & OWEN R.P.) 19 September 1978 (1978-09-19) column 15; example 26	1-7

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
25 September 2000	09/10/2000

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/06825

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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INTERNATIONAL SEARCH REPORT

.formation on patent family members

Inter · onal Application No
PCT/EP 00/06825

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